Claims 8-20 were rejected under the first paragraph of 35 USC § 112. The Examiner stated that the term "soluble" was not supported by the specification and constituted new matter. Applicant respectfully traverses.

Applicant previously noted that the amendment is supported at pages 7-8 and Example 1 of the specification. In particular, the specification points to the method of Wampler, *et al.*, 1985. At page 8 and elsewhere, the specification teaches mixing and blending – physical steps carried out on liquids. Example 1, page 19, line 12 refers to "200 mL of SFP in a glass bottle to which a redox buffer is added and "mixed" (line 14). The specification particularly points to the rHBsAg produced by Wampler after the filtration step. Wampler *et al.*, page 6830, right column, heading "Antigen Purification" describes a process of taking a "crude extract", removing debris by centrifugation, and filtering the supernatant. Applicant is unclear as to how the Examiner reads Wampler *et al.*, after having centrifuged and filtered the solution, to have produced anything other than a solution containing soluble rHBsAg. Therefore, Applicant contends that the term "soluble" is adequately supported by the teaching of the specification.

However, the Examiner relies on a citation to Builder, *et al.*, US 4,620,948 as supporting the notion that the rHBsAg discussed in Applicant's specification can be insoluble. To wit, Builder *et al.*, states:

"A large number of human, mammalian, and other proteins, including, for example, human growth hormone, (hGH) bovine growth hormone (bGH) and a number of interferons have been produced in host cells by transfecting such cells with DNA encoding these proteins and growing resulting cells under conditions favorable to the expression of the new heterologous protein. Viral coat proteins, such as capsid proteins of foot and mouth disease (FMD) virus and the surface antigenic protein of hepatitis B virus (HBsAg) are still other examples of heterologous proteins which have also been produced in suitable recombinant DNA engineered hosts. The **heterologous protein is frequently precipitated** inside the cell, and constitutes a significant portion of the total cell protein." (lines 18-32, **emphasis** added).

Further, Builder *et al.*, contend:

"Various heterologous proteins expressed in bacterial host cells, for example, pGH, hGH, and viral coat proteins such as a fusion protein with FMD virus, protein and HBsAg form refractile bodies **to a greater or lesser extent** under commonly found culture conditions. Certain other proteins such as immune interferon (IIF) and leukocyte interferon (LeIF) are more soluble in the cytoplasm. (Fibroblast interferon (FIF) is, however, refractile in host culture.)" (col. 6, lines 48-56, **emphasis** added)

Finally, Builder *et al.*, states:

"The invention herein is directed to procedures which are useful in isolating, purifying, and, if necessary, reactivating proteins which appear in host cells in the form of "refractile bodies". Part of the invention concerns methods which encourage such refractile body formation; **however, the procedures for protein recovery and activation disclosed herein are intended to be specifically applicable to such refractile proteins**." (col 6, lines 30-37, **emphasis** added)

Builder *et al.*, teach in both Scheme 1 (col 9-10) and Scheme 2 (Col 18), that the in applying the method of their invention, processing the insoluble proteins found in refractile bodies includes steps to centrifuge the cell lysate and discard the supernatant. In direct and opposite contrast, the method of Wampler *et al.*, requires centrifugation and collection of supernatant. Any insoluble protein that may be produced, according to Builder *et al.*, "to a greater or lesser extent," is discarded in the Wampler *et al.*, process.

In view of the above remarks, Applicant believes that the Examiner is incorrect to insist that Builder *et al.*, is appropriately cited, and incorrect in maintaining that "soluble" HBsAg is not supported by the teachings of Applicant's specification. Therefore, Applicant requests withdrawal of the stated rejection.

Rejections under 35 USC § 103

Claims 8-16 and 20 were rejected in view of Builder *et al.*, US 4,620,948. Applicant respectfully traverses.

The Examiner now states that even if the protein is soluble. (With regard to the Examiner's statement that "soluble" is new matter, Applicant incorporates the remarks above.) The Examiner now states that one of skill in the art "would have been motivated to correct misfolding...." (Action at page 4, lines 13-14). Applicant agrees and cites Wampler *et al.*, as an example of the attempts made in the art to improve the folding of HBsAg. However, the Examiner continues and states "Therefore, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing the instant invention because Builder et al., teaches refolding solubilized protein in weaker denaturants and a sulfhydryl compound." (*Id.* At lines 15-18). Applicant disagrees.

Wampler *et al.*, discussed the use of a mixture of oxidized and reduced glutathione to refold proteins. (page 6833, col 2, lines 42-55). Wampler *et al.*, concluded that method did not work to increase disulfide crosslinking in HBsAg and stated that their "results favor an oxidative mechanism for the thiocyanate conversion." (*Id*) Wampler *et al.*, thus

explicitly teaches away. In view of the fact that Builder *et al.*, did not use their technique on HBsAg (soluble or insoluble) and the fact that Wampler *et al.*, teach that the technique did not improve HBsAg, Applicant contends that one of ordinary skill in the art at the time the invention was made would not have had a reasonable expectation of being able to produce the instant invention. Therefore, Applicant requests that the stated rejection be withdrawn.

Claims 17 – 19 were rejected over Builder *et al.*, in view of Petre *et al.*, or Even-Chen. Because neither Petre *et al.*, or Even-Chen make up for the deficiency of Builder *et al.*, as the primary reference, the combinations can not provide the basis for a *prima facie* case of obviousness against the patentability of the present claims. Therefore, Applicant respectfully requests that all of the stated rejections against Claims 17-19 be withdrawn.

CONDITIONAL PETITION

Applicant hereby makes a Conditional Petition for any relief available to correct any defect in connection with this filing, or any defect remaining in this application after this filing. The Commissioner is authorized to charge deposit account 13-2755 for the petition fee and any other fee(s) required to effect this Conditional Petition.

CONCLUSION

Claims 8-20 are now believed to be presented in condition for Allowance. An early indication of the same is requested. The Examiner is invited to contact Applicant's Attorney at the telephone number given below, if such would expedite the allowance of this application.

Respectfully submitted,

By _____

Michael D. Yablonsky, Ph.D.
Reg. No. 40,407
Attorney for Applicant
MERCK & CO., INC.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-4678

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VERSION OF AMENDED CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

20. (TWICE AMENDED) The method according to Claim [17] 8 wherein the incubation in step d is about 60 hours and further comprising the steps of

e) adding an aluminum adjuvant, and

f) co-precipitating the rHBsAg and the adjuvant,

wherein [the incubation is] step f [is] includes an incubation of about 40 hours.